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Heredity of interocular similarities in components of refraction: a population-based twin study among 66- to 79-year-old female twins

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ABSTRACT.

Purpose: To examine genetic influences on interocular similarities in ocular refraction and components of refraction among elderly female twins.

Methods: Refraction was assessed in 94 monozygotic (MZ) and 74 dizygotic (DZ) female twins aged 66–78 years. Absolute values of interocular differences (Aniso variables) in spherical refraction (SR), refractive astigmatism (AST), spherical equivalent (SE), corneal refractive power (CR), corneal astigmatism (CAST), anterior chamber depth (ACD) and axial length (AL) were calculated. The differences between sisters in each of the Aniso variables were calculated and graded into two categories, best differentiating the groups, here isometric and anisometric values. The cut-offs for grading as isometric were AnisoSR < 0.75 D, AnisoAST < 0.5 D, AnisoSE < 1.0 D, AnisoCR < 0.5 D, AnisoCAST < 0.50 D, AnisoACD < 0.1 mm and AnisoAL < 0.1 mm. Genetic influences on these traits were investigated by comparing the prevalence of isometric and anisometric differences between the MZ and DZ pairs in the Aniso variables and the interrelationships between the Aniso variables.

Results: When the Aniso variables were treated as continuous, no significant differences were found between the MZ and DZ subjects. When the proportions of isometric intratwinpair interocular differences in the Aniso variables in the MZ and DZ cotwins were compared, the prevalences (MZ/DZ) were AnisoSR: 68%/60%; AnisoAST: 66%/57%; AnisoSE: 87%/68%; AnisoCR: 83%/78%; AnisoCAST: 69%/35%; AnisoACD: 77%/63%; and AnisoAL: 76%/60%. The differences were statistically significant for Aniso SE ($p = 0.035$, Fisher's exact test) and CAST ($p = 0.007$). The greater homogeneity in the interocular differences between the MZ sisters supports the assumption that isometropia of different elements of refraction is genetically influenced and tending to continue up to older ages. In cases where AnisoSE was <1.0 D, higher CR in one eye was associated with shorter AL ($r = -0.398$, $p < 0.001$), thereby contributing to emmetropization, irrespective of zygosity. In the cases of AnisoSE ≥ 1 D, no similar influence on emmetropization was observed. The difference between sisters in AnisoSE was associated with the intratwinpair difference in Aniso AL, but not with the intratwinpair differences in AnisoCR, irrespective of zygosity.

Conclusion: The higher prevalence of similarities in isometropia of the spherical equivalent and corneal astigmatism between the MZ pairs compared to DZ pairs is consistent with the view that genetic influences on the refractive elements of the eye, tending to isometropia, continue into older age. The interrelation between CR and AL tends to maintain isometropia of SE irrespective of zygosity.

Key words: anisometropia – astigmatism – corneal refraction – emmetropia – isometropia
spherical equivalent

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Introduction

Isometropia is the condition in which both eyes have equal refractive power. Cases of isometropia usually show accumulation around emmetropia (Fleddelius 1980). Typically, a intereye difference of less than one dioptre in spherical equivalent (SE) is considered clinically relevant isometropia of SE. Isometropia is dependent on the process of emmetropization, which tends to maintain binocular vision and symmetry of refraction. In isometropia, a balance is maintained in both eyes between the different refractive components, whereas in anisometropia, this balance is lacking. The clinical consequences of higher values of anisometropia of SE (AnisoSE) and of refractive astigmatism (AST, AnisoAST) are difficulties in fusion and asthenopic symptoms due to aniseikonia. Higher AnisoSE and AnisoAST are also significant causes of amblyopia (Maconachie et al. 2013). The mechanism of AnisoSE is considered to be a consequence of an uneven process of emmetropization during childhood (Vincent et al. 2011). After excluding cases of ocular surgery and traumas, heredity was suggested to be the main cause of higher AnisoSE in most cases (Curtin 1985). However, studies on the heredity of AnisoSE and AnisoAST have mainly focused on the heredity of amblyopia (Ingram & Walker 1979). Although many studies exist on anisometropia and its heredity (Vincent et al. 2011) and case reports among twins have indicated a genetic influence in symmetric AnisoSE (De Jong et al. 1993) or in mirror image AnisoSE (Cidis et al. 1997; Okamoto et al. 2001; Kim et al. 2010), we found no twin studies on the effect of heredity on the different components of refraction and the influence of these on isometropia and anisometropia of spherical equivalent and astigmatism.

Our earlier studies on the present subjects found that 83% of the variance in SE (Pärssinen et al. 2010), one third in AST (Pärssinen et al. 2013a), 81% in corneal refraction (CR) (Pärssinen et al. 2013b) and almost all (over 99%) in axial length (AL) (Pärssinen et al. 2015) were explained by heritable factors. When we studied interocular differences in the same sample, we found emmetropization in AnisoSE; for example, higher CR in the right

eye was associated with shorter AL in the same eye (Pärssinen et al. 2016). The present aim was to investigate the genetic influences on different elements of ocular refraction connected with isometropia in elderly female twins.

Materials and Methods

This study forms part of the Finnish Twin Study on Aging, the purpose of which is to investigate genetic and environmental effects on the disablement process and on vision and refraction in older women. A detailed description of the recruitment process has been published earlier (Kaprio & Koskenvuo 2002; Tiainen et al. 2005; Pärssinen et al. 2010).

In brief, the database of Finnish Twin Cohort Study (started in 1975) contains 13 888 adult twin pairs (Kaprio et al. 1978). Four hundred and fourteen of the 1260 surviving pairs of female twins born 1924–1937 were invited to participate. Two hundred and seventeen pairs [103 monozygotic (MZ) and 114 dizygotic (DZ)] attended the study centre examinations. To be included, both cotwins had to agree to participate. Reasons for nonparticipation were unwillingness of one or both sisters to participate (106 pairs), and disease or poor health status (91 pairs). Zygosity was confirmed by applying a battery of 10 highly polymorphic gene markers at the National Public Health Institute to DNA extracted from a sample of venous blood.

The requisite measurement instruments were not available throughout the study period, and hence, ophthalmic examinations, including measurements of anterior chamber depth (ACD) and AL, could only be performed for 79 MZ and 88 DZ twin pairs. Eyes operated on for cataract and glaucoma were excluded. In 20 eyes, the corneal measurements, and in two eyes the ACD and AL measurements were inaccurate, mostly due to poor fixation, and hence, these values were excluded. After exclusions, 94 MZ and 74 DZ twins remained for analysis. Mean subject age was 70.7 years ($SD \pm 3.1$), ranging from 66 to 78 years. The study was approved by the ethics committee of the Central Hospital of Central Finland, and both twins gave their informed consent. Our research adhered to the tenets of the Declaration of Helsinki.

Examination

Refraction, without cycloplegia, was measured with an autorefractor (Topcon AT, Tokyo, Japan) and controlled subjectively by the red–green test. Mean CR, corneal astigmatism (CAST), ACD and AL were measured with an IOL Master (Carl Zeiss, Jena, Germany). The measurements were performed by a trained nurse. The examination was performed for both twin sisters by the same nurse, but on separate occasions, during the 1-day assessment in a laboratory at the University of Jyväskylä. The nurse was not aware of the zygosity of the twins.

Absolute values of the interocular differences in spherical refraction (AnisoSR), spherical equivalent (AnisoSE), astigmatism (AnisoAST), corneal refraction (AnisoCR), corneal astigmatism (AnisoCAST), anterior chamber depth (AnisoACD) and axial length (AnisoAL) were calculated. The differences between the sisters in the Aniso variables were calculated and categorized as isometropic and anisometropic. The cut-offs for grading, here regarded as isometropic, were $AnisoSR < 0.75$ D, $AnisoAST < 0.5$ D, $AnisoSE < 1.0$ D, $AnisoCR < 0.5$ D, $AnisoCAST < 0.50$ D, $AnisoACD < 0.1$ mm and $AnisoAL < 0.1$ mm. The distribution of each variable was compared between MZ and DZ twin pairs. The lower twin pair differences dominated among MZ and higher among DZ. The cut-offs for binary grading for the Aniso variables were selected as they best differentiated the variables between MZ and DZ for the present analyses of this study.

When calculating the interdependencies between the interocular differences in SE, CR and AL, the real differences (not absolute values) between the right and left eye were used. Using the real values enabled comparison of the corresponding lateralities for the Aniso variables. Positive Aniso variables indicated higher values for the right eye and negative Aniso variables higher values for the left eye.

Analytical methods

The adjusted Wald test was used to test the equality of the means of the normally distributed continuous variables (all the original refraction and axial variables were normally distributed).

The non-normally distributed difference in the absolute Aniso variables between the MZ and DZ twins and between cotwins was tested using the Mann–Whitney test (Table 1 and Fig. 1). Within-pair analyses were used for testing differences between the right and left eye. The difference between the zygotic groups in the proportions of nonsignificant twin pair interocular differences was tested using cross-tabulation (2×2 tables) and Fisher’s exact test (Table 2). Associations between non-normally distributed variables were analysed using Spearman’s rank correlation coefficients. The differences between MZ and DZ twin pairs for the Aniso variables were tested using the Wilcoxon signed-rank test. Statistical analyses were performed using IBM SPSS STATISTICS version 24 and R package lme4 version

1.1-12 (Wilhelm & Manjunath 2010). The level of statistical significance was set at $p < 0.05$.

Results

Mean SE in the study population was hyperopic. Myopic refraction ($SE \leq -0.5D$) was present in both eyes in 9.5% of twins. The means \pm standard deviations for spherical refraction (SR), AST and SE of the right eye were $+1.45 \pm 1.47 D$, $0.76 \pm 0.50 D$ and $+1.67 \pm 1.70 D$, respectively, with no significant differences in means between the right and left eye. The respective means of the right eye for CR, CAST, ACD and AL were $44.51 \pm 1.14 D$, $0.81 \pm 0.45 D$, $3.10 \pm 0.27 mm$ and $22.97 \pm 0.80 mm$, with no significant differences between the right and left eye.

Table 1 shows the interocular differences in the studied variables for all the twins. Anisometropia of $SE \geq 1 D$ and $\geq 2 D$ was present in 19.7% and 5.4% of cases, respectively, and AnisoAST $\geq 1 D$ and $\geq 2 D$ in 8.9% and 1.2% of cases. No statistically significant differences were observed in these variables between the zygosity groups.

Between-sister differences in the Aniso variables

In this study, the Aniso variables were calculated to determine intrapair similarities and differences in between MZ and DZ cotwins. Figure 1 shows the mean values of the between-sister differences in the Aniso variables for the MZ and DZ twins separately. While all the means, except for AnisoACD, were smaller among the MZ twins, the only significant difference was in AnisoCAST ($p = 0.023$).

Next, the between-sister differences in the Aniso variables were categorized into two groups: isometropic and anisometropic. Table 2 shows the proportions of nonsignificant (isometropic) interocular differences for the MZ and DZ twin sisters. More similarities in isometropia were observed in all the variables between the MZ than DZ twin sisters, but the differences between the zygosity groups were significant only for AnisoSE ($p = 0.035$) and AnisoCAST ($p = 0.006$).

Analysis of the interdependencies of the differences in the Aniso variables between sisters showed that the difference in AnisoSE was significantly associated with the difference in AnisoAL in both the MZ and DZ sisters, but not with the difference in AnisoCR (Table 3). The between-sister difference in AnisoAST correlated significantly with that found for AnisoCAST, when both zygosity groups were analysed together. The greater difference between the sisters in AnisoCAST was, in turn, associated with a greater difference in AnisoCR. These correlations were not indicative of the influence of heredity.

When comparing the real interocular differences in CR and AL (value for right eye – left eye), significant correlations were observed in both zygosity groups, with no significant difference between the MZ and DZ twins (Table 4). However, the correlation was significant only if AnisoSE were $< 1 D$.

Table 1. Means \pm standard deviations (SD) and maximum values of interocular differences among the study subjects.

	N	Mean (SD)	Maximum value
AnisoSR (D)	168	0.59 (± 0.59)	3.75
AnisoAST (D)	168	0.39 (± 0.39)	2.50
AnisoSE (D)	168	0.59 (± 0.61)	3.88
AnisoCR (D)	142	0.33 (± 0.31)	2.15
AnisoCAST (D)	142	0.37 (± 0.37)	3.18
AnisoACD (mm)	166	0.09 (± 0.14)	1.14
AnisoAL (mm)	166	0.13 (± 0.12)	0.91

Aniso = interocular difference in ACD = anterior chamber depth; AL = axial length; Ast = refractive astigmatism; CAST = corneal astigmatism; CR = corneal refraction; D = dioptre; SE = spherical equivalent; SR = spherical refraction.

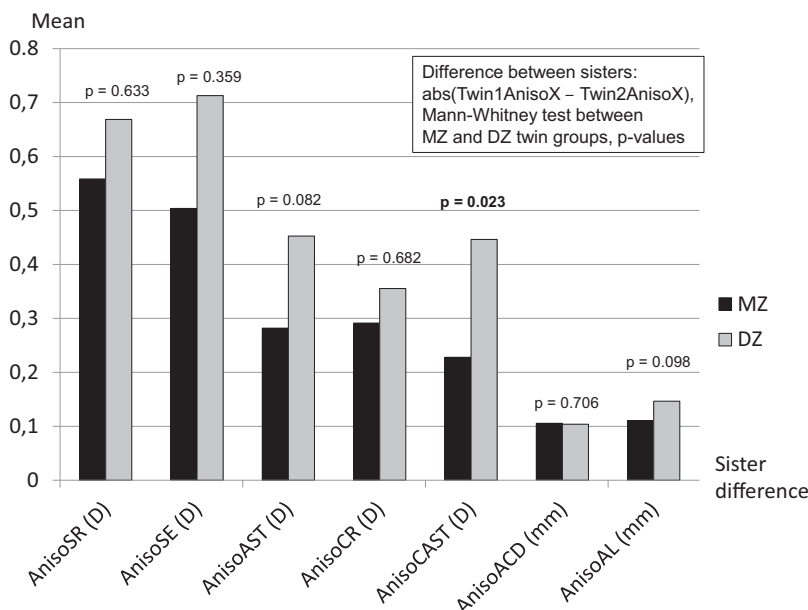


Fig. 1. Mean differences between sisters for interocular differences among monozygotic (MZ) and dizygotic (DZ) twins. ACD = anterior chamber depth; AL = axial length; Aniso = anisometropia; AST = refractive astigmatism; CAST = corneal astigmatism; CR = corneal refractive power; SE = spherical equivalent; SR = spherical refraction.

Discussion

Initially, we sought to identify genetic components explaining anisometropia of SE and AST, and the associations of these genetic components with different interocular differences in the components of refraction. However, the correlations (ICC) found were very weak, and in some instances negative, rendering it impossible to construct a reliable model that would explain the heredity of AnisoSE or AnisoAST by the interrelationships between the variables studied. One obvious reason for this was the low prevalence of cases of higher anisometropia. In fact, the prevalence of higher AnisoSE in our study was lower than reported in many other studies. For example, in the study by Mohammadi et al. (2013) conducted among 60- to 64-year-olds,

AnisoSE ≥ 3 D was 3.4%, whereas the respective prevalence in our materials was 1.2%.

Instead, comparison of the differences between the twin pairs in the studied Aniso variables (as continuous variables) revealed that the MZ sisters exhibited more similarities than the DZ sisters, although comparison of the intratwinpair differences between the zygosity groups showed that these were significant only for AnisoCAST (Fig. 1). In a larger study population, the differences observed in some of the other Aniso variables might have reached the level of significance. Theoretically, differences of zero between MZ cotwins would indicate no environmental influences; however, this would be exceptional as measurement error induces differences, both between the cotwins in a MZ pair and between

repeated measurements of the same individual.

In this study, the grading of Aniso variables to nonsignificant (isometric) and significant (anisometric) was done empirically by comparing the distributions of each variable among MZ and DZ twins and twin pairs and thus finding limits for each variable best differentiating MZ and DZ twins for the purposes of this study. Comparison of the differences between the cotwins as dichotomous revealed that the similarities in isometric values between the twin sisters were higher for all the studied variables in the MZ group. However, in the present data, the differences reached the level of significance for only AnisoSE and AnisoCAST. The lower differences observed between the MZ compared to DZ sisters can be interpreted as evidence of hereditary influence in maintaining interocular isometropia. The main factor explaining the difference between sisters in AnisoSE was the difference between them in AnisoAL, which was, however, independent of zygosity. Many studies of anisometric myopia have shown that AL asymmetry has a strong correlation with anisometropia (Fledelius 1980; Hashemi et al. (2013); Pärssinen & Kauppinen 2017; Singh et al. 2017).

In this investigation of the factors explaining isometropia, the real differences between the right and left eye,

Table 2. The proportions of nonsignificant (isometric) twin pair interocular differences among monozygotic (MZ) and dizygotic (DZ) female twins.

Aniso variables with cut-offs of significance (isometric value)	MZ pairs % (n/N)	DZ pairs % (n/N)	Fisher's exact p-value
AnisoSE < 1.00 D	87.2 (41/47)	67.6 (25/37)	0.035
AnisoAST < 0.50 D	66.0 (31/47)	56.8 (21/37)	0.498
AnisoSR < 0.75 D	68.1 (32/47)	59.5 (22/37)	0.494
AnisoCR < 0.50 D	83.3 (35/42)	77.8 (21/27)	0.753
AnisoCAST < 0.50 D	69.0 (29/42)	34.5 (10/29)	0.007
AnisoACD < 0.10 mm	77.3 (34/44)	62.9 (22/35)	0.214
AnisoAL < 0.10 mm	58.7 (27/46)	37.1 (13/35)	0.073

n/N = number of pairs with nonsignificant interocular difference in zygotic group/number of all pairs in zygotic group.

Table 3. Interdependencies (Pearson correlations) between the intrapair differences in spherical equivalent (AnisoSE), corneal refraction (AnisoCR), axial length (AnisoAL), astigmatism (AnisoAST) and corneal astigmatism (AnisoCAST).

Between-sister differences	MZ			DZ			MZ and DZ combined		
	N	R	p	N	R	p	N	R	p
AnisoSE by AnisoCR	42	-0.113	0.476	29	0.229	0.233	71	0.124	0.304
AnisoSE by AnisoAL	47	0.442	0.003	36	0.452	0.006	83	0.447	<0.001
AnisoAST by AnisoCAST	42	0.222	0.157	29	0.203	0.292	71	0.263	0.027
AnisoCAST by AnisoCR	42	0.504	0.001	29	0.324	0.087	71	0.380	0.001

Significant correlation bolded.

Table 4. Correlations (Pearson) of the real interocular differences (value of right eye – left eye) in corneal refraction (CR) and axial length (AL) at different anisometric level of spherical equivalent (AnisoSE).

	Correlation between real interocular differences in CR and AL								
	MZ			DZ			MZ and DZ combined		
	N	R	p	N	R	p	N	R	p
All cases of AnisoSE	112	-0.246	0.009	99	-0.270	0.007	211	-0.258	<0.001
AnisoSE < 1.0 D	96	-0.347	0.001	72	-0.465	<0.001	168	-0.398	<0.001
AnisoSE ≥ 1.0 D	16	0.101	0.710	27	-0.114	0.572	43	-0.076	0.629

Significant correlation bolded.

rather than absolute values, were used. A significant correlation was observed between the real interocular differences in CR and AL in cases where AnisoSE was <1.0 D ($r = -0.398$, $p < 0.001$). Thus, for example, higher CR in the right eye was associated with longer AL in the left eye, resulting in isometropia of SE. The same correlation was non-significant in cases where AnisoSE was ≥ 1.0 D. Thus, it seems that the influence on emmetropization of the balance between CR and AL in isometropia continues up to a difference between the eyes of around 1 D. Two earlier studies have shown a similar process of emmetropization in anisometropia of SE (Pärssinen et al. 2016; Pärssinen & Kauppinen 2017). However, the present study found no significant difference between the zygosity groups in emmetropization.

The results of this investigation indicated that a greater difference between sisters in CR was associated with a greater difference in CAST and that this in turn was associated with a greater difference in refractive astigmatism. However, although the difference between sisters in CAST was significantly smaller among the MZ sisters, a corresponding difference between the two zygosity groups was not seen in AST. Residual astigmatism has a significant influence on refractive astigmatism (Mohammadpour et al. 2016). Residual astigmatism, which was not measured in this study, may be the reason for the nonsignificant impact of heredity on AST despite the influence of heredity found for CAST.

Anisometropia of SE has been shown to increase with age (Attebo et al. 1999; Guzowski et al. 2003; Hashemi et al. 2011; Ostadimoghaddam et al. 2012). In elderly subjects, a significant part of that increase can be explained by age-related changes in the lens and the presence of cataract (Mohammadi et al. 2013). In our study, while eyes operated on for cataract were excluded, the thickness of the lens and its refractive power were not recorded, and hence, the possible influence of age-related changes in the lens cannot be determined from our results. Thus, it seems that the hereditary mechanisms tending to maintain isometropia in SE remain present in older age irrespective of possible age-related changes in the lens.

We suggest that twin studies among younger subjects would yield more information on the influence of genetic factors on the different elements of isometropia and on the interactions between the different elements of refraction that, hypothetically, tend to maintain isometropia. To explore the possible influence of heredity on interocular differences in the refractive components that are associated with anisometropia would need a larger number of subjects with higher anisometropia and hence a larger twin sample.

Conclusion

The greater intratwin pair similarity in the Aniso variables observed in the MZ compared to DZ twin sisters indicates that the influence of heredity on isometropia continues into older age. Our data did not allow determination of the impact of heredity on anisometropia.

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